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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,454	10/15/2001	Mark D. Erion	030727.0027.CON1	5123

36183 7590 04/14/2004

PAUL, HASTINGS, JANOFSKY & WALKER LLP
P.O. BOX 919092
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EXAMINER	
JONES, DAMERON LEVEST	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,454	ERION ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *168-185* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *168-185* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *16*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

ACKNOWLEDMENTS

1. The Examiner acknowledges receipt of Paper No. 14, filed 2/2/04, wherein an acceptable RCE (request for continued examination) was filed and an supplemental IDS (information disclosure statement) were submitted.

Note: Claims 168-185 are pending.

COMMENTS/NOTES

2. Review of the application has deemed the following new grounds of rejection necessary in order to clarify the instant invention.

112 FIRST PARAGRAPH REJECTIONS

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 168-185 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims fail to comply with the written description requirement because of the variable M definition. In particular, the phrase 'M is selected form the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active in vivo and that is attached to

the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom, with the proviso that M-PO_3^{2-} is not an FBPase inhibitor' (see independent claims 168 and 180-185) does not disclose what biologically active compounds the invention encompasses. There is/are no structure(s) to determine what agents Applicant are claiming to be compatible with the instant invention. The specification discloses limited exemplification of specific M species (i.e., M is the compound of formulae II (page 59) , III (page 60), and IV (page 61), or a nucleoside (page 74, lines 13-25)) that are encompassed by the instant invention while the claims are directed to any and all possible biologically active agents. In addition, the specification and claims does not distinguish what are the FBPase inhibitors. Thus, since the specification and claims do not contain a clear and concise description, a written description rejection is proper.

112 SECOND PARAGRAPH REJECTION

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 168-185 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 168-185: The claims as written are ambiguous because it is unclear what is encompassed by Applicant's variable M. Specifically, the phrase 'M is selected form the group that, attached to PO_3^{2-}, $P_2O_6^{3-}$, or $P_3O_9^{4-}$, is biologically active in vivo and that is attached to the phosphorus atom in Formula I via a carbon, oxygen, or nitrogen atom,

with the proviso that M-PO_3^{2-} is not an FBPase inhibitor' (see independent claims 168 and 180-185) is confusing. In particular, it is unclear what biologically active compound(s) Applicant is claiming that are compatible with the instant invention. Is Applicant claiming all possible biological agents? What does Applicant mean by the phrase 'with the proviso that 'M-PO_3^{2-} is not an FBPase inhibitor'? What limitations/conditions has Applicant set forth to distinguish whether M-PO_3^{2-} is not an FBPase inhibitor or not? Hence, it is unclear which compound(s) Applicant is excluding from the claim. Applicant is respectfully requested to the clarify the claims in order that one may readily ascertain what is being claimed.

Claims 169-173, 177, and 179 recite the limitation "wherein MH is" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Did Applicant intend to write "wherein M is" instead of "wherein MH is"?

ADDITIONAL COMMENTS/NOTES

7. It should be noted that no prior art has been cited against Applicant's claims. However, Applicant must address and overcome the 112 rejections above. In particular, the claims are distinguished over the prior art of record because the prior art neither anticipates nor renders obvious a composition comprising the phosphorus cyclic structure wherein the biologically active agent is that of Formula II-IV or a nucleoside.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (571) 272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

D. L. Jones
Primary Examiner
Art Unit 1616

April 13, 2004

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet	1	of	3

Applicant's Copy

Examiner Initials*	Cite No.[1]	U.S. Patent Document Number	Kind Code[2] (if known)	Name of Pa of Cit		
	AA	6,054,587	1	Reddy et		
	AB	6,110,903	1	Kasibhat		
	AC	6,284,748	1	Dang et a		
	AD	6,294,672	1	Reddy et		
	AF	6,399,782	1	Kasibhatla et al.	06/04/02	
	AE	6,489,476	1	Dang et al.	12/03/02	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Office[3]	Number[4]	Kind Code[5] (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T[6]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
		Beaucage and Iyer, "The Synthesis of Modified Oligonucleotides by the Phosphoramidite Approach and Their Applications," Tetrahedron, 49(28):6123-6194 (1993).	
		Borch and Millard, "The Mechanism of Activation of 4-Hydroxycyclophosphamide," J. Med. Chem., 30:427-431 (1987).	
		Cooper et al., "Use of Carbohydrate Derivatives for Studies of Phosphorus Stereo-chemistry. Part II. Synthesis and Configurational Assignments of 1,-3,2-Oxathiaphosphorinan-2-ones and 1,3,2-Dioxaphosphorinan-2-thiones," J.C.S. Perkin I, 3/2422:1049-1052 (1973).	
		Clercq et al., "A Novel Selective Broad-spectrum Anti-DNA Virus Agent," Nature, 323:464-467 (1986).	

Examiner Signature		Date Considered	4/8/04

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation is not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] Unique citation designation number. [2] See attached Kinds of U.S. Patent Documents. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 3

Complete If Known	
Application Number	09/978,454
Filing Date	October 15, 2001
First Named Inventor	Erion et al.
Group Art Unit	1616
Examiner Name	Dameron Jones
Attorney Docket Number	032465.00027.RCE2(CON1)

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		Farquhar et al., "Synthesis and Antitumor Evaluation of Bis[(pivaloyloxy)methyl] 2'-Deoxy-5-fluorouridine 5'-Monophosphate (FdUMP): A Strategy to Introduce Nucleotides into Cells," J. Med. Chem., 37:3902-3909 (1994).	
		Friis and Bundgaard, "Prodrugs of Phosphates and Phosphonates: Novel Lipophilic α-acyloxyalkyl Ester Derivatives of Phosphate- or Phosphonate Containing Drugs Masking the Negative Charges of these Groups," Euro. J. Pharm. Sci., 4:49-59 (1996).	
		Harada et al., "Resoluation of 1,3-alkanediols Via Chiral Spiroketals Derived from t-Menthone," Tetrahedron, 28(41):4843-4846 (1987).	
		Khorana et al., "Cyclic Phosphates. III. Some General Observations on the Formation and Properties of Five-, Six- and Seven-membered Cyclic Phophate Esters," Brit. Col. Res. Couns., 79:430-436 (1957).	
		Korba et al., "Liver-targeted Antiviral Nucleosides: Enhanced Antiviral Activity of Phosphatidyl-dideoxyguanosine Versus Dideoxyguanosine in Woodchuck Hepatitis Virus Infection *In Vivo*," Hepatology, 23(5):958-963 (1996).	
		Lefebvre et al., "Mononucleoside Phosphotriester Derivatives with *S*-acyl-2-thioethyl Bioreversible Phosphate-protecting Groups: Intracellular Delivery of 3'azido-2',3'dideoxythymidine 5'-monophosphate," J. Med. Chem., 38:3941-3950 (1995).	
		Ludeman et al., "Synthesis and Antitumor Activity of Cyclophosphamide Analogues. 4. Preparation, Kinetic Studies, and Anticancer Screening of "Phenylketophosphamide" and Similar Compounds Related to the Cyclophosphamide Metabolite Aldophosphamide," J. Med. Chem., 29:716-727 (1986).	
		McGuigan et al., "Intracellular Delivery of Bioactive AZT Nucleotides by Aryl Phosphate Derivatives of AZT," J. Med. Chem., 36:1048-1052 (1993).	
		Mosbo and Verkade, "Dipole Moment, Nuclear Magnetic Resonance, and Infrared Studies of Phosphorus Configurations and Equilibria in 2-R-2-Oxo-1,3,2-dioxaphosphorinanes," J. Org. Chem., 42(9):1549-1555 (1977).	
		Nakayama and Thompson, "A Highly Enantioselective Synthesis of Phosphate Triesters," J. Am. Chem. Soc., 112:6936-3942 (1990).	

Examiner Signature		Date Considered	4/8/04

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Sheet 3 of 3

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First Named Inventor	Erion et al.
Group Art Unit	1616
Examiner Name	Dameron Jones
Attorney Docket Number	032465.00027.RCE2(CON1)

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		Ramachandran et al., "Efficient General Synthesis of 1,2- and 1,3-diols in High Enantiomeric Excess via the Intramolecular Asymmetric Reduction of the Corresponding Ketoalkyl Diisopinocampheylborinate Intermediates," Tetrahedron, 38(5):761-764 (1997).	
		Starrett, Jr. et al., "Synthesis, Oral Bioavailability Determination, and *in Vitro* Evaluation of Prodrugs of the Antiviral Agent 9-[2-(Phosphonomethoxy)ethyl]adenine (PMEA)," J. Med. Chem., 37:1857-1864 (1994).	
		Thompson et al., "Synthesis, Bioactivation and Anti-HIV Activity of the Bis(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Esters of the 5'-monophosphate of AZT," J. Chem. Soc., 2/06723D:1239-1245 (1993).	
		Weber and Waxman, "Activation of the Anti-cancer Drug Ifosphamide by Rat Liver Microsomal P450 Enzymes," Biochem. Pharm., 45(8):1685-1694 (1993).	
		Zon et al., "NMR Spectroscopic Studies of Intermediary Metabolites of Cyclophosphamide. A Comprehensive Kinetic Analysis of the Interconversion of *cis*- and *trans*-4-Hydroxycyclophosphamide with Aldophosphamide and Concomitant Partitioning of Aldophosphamide Between Irreversible Fragmentation and Reversible Conjugation Pathways," J. Med. Chem. 27:466-485 (1984).	

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